Remarks

Claims 1, 5-9, 14, 20, 22-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-53, 55-59, 69, and 70 are pending.

Rejections Under 35 USC § 103

1. Claims 1, 5-9, 14, 20, 22-25, 27, 29, 31, 33, 35-38, 39, 41, 44-49, 51-53, 55-58, 69 and 70 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), Navarro et al. (J. Virol. Meth., vol. 56, pp59-66, 1996) and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989). Applicant respectfully traverses this rejection.

Lizardi discloses a method of rolling circle amplification (RCA) involving replication of single-stranded DNA molecules (see column 19, lines 21-23). Lizardi discloses use of a rolling circle replication primer of defined sequence that hybridizes to an amplification target circle (ATC) followed by rolling circle replication of the ATC primed by the rolling circle replication primer to produce a tandem sequence DNA (see column 19, lines 20-31). Lizardi fails to disclose or suggest explicitly the use of primers having random sequence, fails to disclose or suggest directly hybridization of a plurality of primers to each amplification target circle and fails to disclose or suggest directly formation of multiple tandem sequence DNA products by extension of multiple primers.

Landers et al. discloses PCR methods of genotyping including degenerate oligonucleotide primed-PCR (DOP-PCR) and arbitrarily primed PCR (AP-PCR) (see column 15, line12 – column 16, line 26 and column 17, lines 28-29). AP-PCR utilizes short oligonucleotides with defined sequences that are arbitrarily selected as PCR primers to amplify a discrete subset of portions of a high complexity genome (see column 17, lines 28-33 of Landers et al.).

Navarro et al. discloses PCR-based methods for amplifying sequence present in small circular RNAs.

Eckstein et al. discloses nuclease resistant primers.

Claims 1, 5-9, 14, 20, 22-25, 27, 29, 31, 33, 35-38, 39, 41, 44-49, 51-53, 55-58, 69 and 70 are drawn to a process for selectively amplifying nucleic acid sequences. The process

involves contacting multiple single stranded non-circular random oligonucleotide primers (P1) and one or more single stranded amplification target circles, where each ATC hybridizes to a plurality of the P1 primers, under conditions that promote rolling circle replication of the amplification target circle by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products. Thus the claims require amplification of a nucleic acid sequence that involves the use of single stranded amplification target circles, hybridization of a plurality of P1 primers of random sequence to each ATC under conditions that promote rolling circle replication of the ATC by extension of the P1 primers to form multiple TS-DNA products by extension of the P1 primers. As such, the amplification of the nucleic acid sequence is a product of rolling circle amplification primed at different sites on the template ATC and results in multiple TS-DNA products by extension of the P1 primers.

In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office has the burden under § 103 to establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The present claims require the use of random primers for priming rolling circle replication of single stranded amplification target circles. The Office Action alleges (page 11, lines 1-4) that it would have been *prima facie* obvious to one of ordinary skill in the art to have included the random PCR primers of arbitrary, defined sequences in the method of Lizardi. The Office Action argues that those of skill in the art would have been motivated to do so because Landers et al. allegedly provides that random primers allow amplification of unknown DNA

sequences. Applicants disagree. Landers et al. neither discloses nor suggests random primers as claimed. In addition, the design of the primers of Landers et al. is a poor match for the method of Lizardi, making it unlikely that those of ordinary skill in the art would consider using the primers of Landers et al. in the method of Lizardi.

The Office Action alleges, in part, at page 6, lines 22- page 7, line 2, that Lizardi teaches a method of amplification comprising contacting multiple single stranded non-circular random oligonucleotide primers (P1), one or more single stranded smplification target circles (ATCs) under conditions where each ATC hybridizes to a plurality of said P1 primer, wherein said conditions promote rolling circle replication of said ATC by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products. The Office Action admits that Lizardi et al. does not teach random primers (See Office Action page 10, line 1).

In support its interpretation of Lizardi, the Office Action (page 5 and page 7) cites column 25, lines 36-57 as well as column 28, lines 8-18 of Lizardi et al., which describe strand displacement cascade amplification (SDCA). The Office Action alleges that SDCA teaches the use of multiple primers hybridizing to and priming rolling circle replication of an ATC. This is not the case. SDCA begins with rolling circle replication of an ATC primed by a rolling circle replication primer to form TS-DNA. Secondary strand displacement is accomplished by hybridizing secondary DNA strand displacement primers to TS-DNA (See Lizardi et al. column 25, lines 24-28). Secondary DNA strand displacement primers hybridize to, and prime replication of, TS-DNA to form what is termed TS-DNA-2. The secondary DNA strand displacement primers have sequence matching part of the OCP or ATC used to generate TS-DNA (See column 12, lines 21-29), therefore, by definition, they do not bind to the ATC (See Lizardi et al. column 25, lines 43-45). Tertiary DNA strand displacement primers then hybridize to, and prime replication of the TS-DNA-2 generated from the replication of the initial TS-DNA, primed by the secondary DNA strand displacement primers to form TS-DNA-3 (See Lizardi et al., column 27, lines 2-4). While it is true that the methods of Lizardi generically encompass the use of multiple primers and that in some embodiments of the methods of Lizardi the use of rolling circle replication primers and tertiary DNA strand displacement primers together might

result more than one primer hybridizing to a single amplification target circle, Lizardi does not specifically disclose and certainly does not suggest the use of multiple rolling circle replication primers nor formation of multiple tandem sequence DNA products from multiple primings of a single amplification target circle. It is clear that the mere fact that certain subject matter is disclosed within a broader generic disclosure does not make obvious the specific subjected matter not specifically disclosed. In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550 (Fed. Cir. 1994). In the case of an obviousness rejection, an inherent but obscure feature of a reference cannot provide any suggestion or motivation to use such a feature in combination with other references. The cited references must suggest what is claimed, not merely inherently disclose disparate elements of the claimed invention, which is all that the present rejection provides. None of Landers et al., Navarro et al. and Eckstein et al. provide any disclosure or suggestion regarding rolling circle replication and thus do not provide any suggestion to focus the method of Lizardi on the claimed use of multiple primers and multiple primings.

The Office Action also alleges at page 10, lines 5-7, that Landers et al. teaches the use of "multiple arbitrary (= random) primers" to amplify double-stranded DNA circles (YACs). This is not the case. Landers et al. does not disclose random primers as claimed. The Office Action cites column 17, lines 28-42 and 60-64, of Landers which describes a method for generating a reduced complexity genome (RCG) referred to as arbitrarily primed PCR (AP-PCR). The Office Action incorrectly equates the arbitrary primers of Landers et al. to the claimed random primers. The arbitrary primers of Landers et al. are not random. While the primers of Landers et al. have sequence that is arbitrarily chosen, the primers have a specific, non-random sequence. As Landers et al. notes, the primers used in AP-PCR are similar to the DOP-PCR primers with the exception that the AP-PCR primers consist only of the arbitrarily-selected nucleotides and not the 5' flanking degenerate residues or the tag present in primers for DOP-PCR (see column 17, lines 35-39). The arbitrarily-selected nucleotides of the AP-PCR primers are equivalent to the "TARGET" nucleotide sequence of the DOP-PCR primers. As Landers et al. notes (column 15, lines 18-20), the "'TARGET' nucleotide sequence includes at least 5 arbitrarily selected nucleotide residues that are the same for each primer of the set." Thus, the primers of Landers et

al. are not random and thus are not the same as the claimed primers. Therefore, Landers et al. fails to disclose or suggest primers of random sequence. Accordingly, Landers et al. cannot cure the deficiency in Lizardi.

Neither Navarro et al. (cited for disclosure of amplification of single-stranded RNA) nor Eckstein et al. (cited for disclosure of modified nucleotides) cure the deficiencies in Lizardi and Landers et al. discussed above. Accordingly, for all of the above reasons, Lizardi, Landers et al., Navarro et al., and Eckstein et al., either alone or in combination, fail to make obvious claims 1, 5-9, 14, 20, 22-25, 27, 29, 31, 33, 35-38, 39, 41, 44-49, 51-53, 55-58, 69 and 70. As such, Applicant respectfully requests withdrawal of this rejection.

2. Claims 32, 42 and 59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), Navarro et al. (J. Virol. Meth., vol. 56, pp59-66, 1996) and Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989) and in further view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554, 1992). Applicant respectfully traverses this rejection.

Claims 32, 42 and 59 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi, Landers et al., Navarro et al., and Eckstein et al. in the same way and for the same disclosure for which Lizardi, Landers et al., and Eckstein et al. were applied in the rejection of claims 1, 5-9, 14, 20, 22-25, 27, 29, 31, 33, 35-38, 39, 41, 44-49, 51-53, 55-58, 69 and 70 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi, Landers et al., Navarro et al., and Eckstein et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Skeera et al. fails to supplement this gap in Lizardi, Landers et al., Navarro et al., and Eckstein et al.

Skerra et al. was cited for disclosure of incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'->5' exonuclease activity of DNA polymerases such as Vent and Pfu and use of a mixture of exonuclease-sensitive and

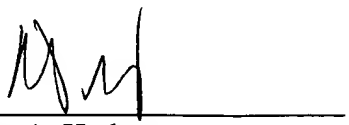
exonuclease-resistant primers in the amplification reaction. This does not supply what is missing from Lizardi, Landers et al., Navarro et al., and Eckstein et al. Thus, Lizardi, Landers et al., Navarro et al., Eckstein et al., and Skeera et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of random sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al., Navarro et al., Eckstein et al., and Skeera et al. fail to make obvious claims 32, 42 and 59. Applicant respectfully requests withdrawal of this rejection.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $225.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(2), and a Request For Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



Robert A. Hodges
Reg. No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer No. 23859

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges

Date 3/27/2006